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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,023	CHEN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-74* is/are pending in the application.

4a) Of the above claim(s) *33-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Action is responsive to Applicants amendment and remarks filed August 16, 2005. Claims 1, 2, 4,7-8 and 23 have been amended. Claim 3 is cancelled. Claims 33-74 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejection Withdrawn

3. In view of Applicant's amendment the rejection under 35 U.S.C. 112, second paragraph, pages 2-3, paragraph 4 is withdrawn.

Rejections Maintained

4. The rejection under 35 U.S.C. 102(e) as anticipated by Hultrgren et al is maintained for claims 1, 5-9, 14-16, 18-21 and 29 for the reasons set forth on pages 3-4, paragraph 4 of the previous Office Action.

The rejection was on the grounds Hultgren et al teach a method for identifying a potentially therapeutically useful substance capable of interacting with a periplasmic molecular chaperone thereby preventing or inhibiting the interaction between a periplasmic molecular chaperone and a pilus subunit (column 10). Hultgren et al teach that the periplasmic chaperone or analogue thereof is in solubilized form (column 10). Hultgren et al teach that the measurement of the degree of binding can be determined *in vitro* by methods such as microcolormetric, radioimmunoassays and enzyme based assays (column 6). Hultgren et al teach that in instances wherein labeled substances, chaperones or antibodies are used, the label could be a radioactive label, a fluorescent

or light absorbing label, an enzyme such as horseradish peroxidase, a ligand such as biotin or any other conventional labeling system known those skilled in the art (column 12). Hultgren et al teach that the binding between chaperones and pilus subunits are obtained by the interaction between the PapD chaperone in *E. coli.* (column 8). Since the interaction between the chaperones and pilus subunits takes place in the periplasmic space the nucleic acid sequences encoding the chaperones would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that the cited reference does not teach or suggest all the claimed limitations. Applicant urges no embodiments of Hultgren et al teach selecting said bacterium based on the presence of said label ligand within in the periplasm wherein said ligand and said candidate binding protein are bound in said bacterium. Applicant urges that none of the asserted teachings of Hultgren et al show or suggest selection of a bacterium based on the presence of a labeled ligand within the periplasm as required by the claims. Applicant urges that Hultgren et al relates to a fundamentally different method than the claimed method and accordingly teaches different steps. Applicant urges that the *in vitro* assays as disclosed in column 6 of the prior art do not suggest selection of a bacterium based on the presence of a labeled in the periplasm of the bacterium. Applicant urges that it is the burden to state with clarity the basis of the rejection.

Applicant's arguments filed August 16, 2005 have been fully considered but they are not persuasive. It is the Examiner's position that Hultgren et al teach the claimed

method. Hultgren et al teaches that gram-negative bacteria require the functions of periplasmic chaperones (column 6). Hultgren et al teach that periplasmic chaperones (candidate binding proteins) are in solubilized form (column 10). Hutrgren et al teach contacting the bacterium with a pilus subunit (target ligand)(columns 10 –11). Hultgren et al teach that the pilus subunit or equivalent may be labeled (e.g. labeled ligand). Hultgren et al teach that the periplasmic chaperone bound to the labeled ligand may be detected by the label ligand which constitutes a type of selection (column 11). Therefore, the bacterium containing the periplasmic chaperone bound to the labeled ligand is selected because it is detected by the labeled ligand. Thus, the claimed method step of selecting a bacterium is taught by the prior art.

To address Applicant's comments regarding the prior art reference not teaching all claim limitations, it should be noted that the prior art reference teaches "identifying" and "detecting" the periplasmic chaperone bound to the labeled ligand. These constitute forms of selecting. Therefore, Hultgren et al teach the claimed method step of "selecting the said bacterium based on the presence of said ligand...". It should be noted that "selection" (i.e. identifying) is the last step the claimed method.

Moreover, Applicant has provided no side-by-side comparison to show that the claimed method differs from that of the prior art. Consequently, it is the position of the Examiner that Hultgren et al anticipate the claimed invention.

5. The rejection under judicially created doctrine of obviousness-type double patenting is maintained for claims 1-2 and 4-32 for the reasons set forth on pages 6-7, paragraph 6 of the previous Office Action.

The rejection was on the grounds that claims 1-2 and 4-32 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-38 and 43-48 of copending Application No. 10/620,278. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein that are capable of a target ligand comprising the steps of: (a) providing a gram-negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in the periplasm of said bacterium, (b) contacting said bacterium with a labeled ligand and (c) selecting said bacterium based on the presence of said labeled ligand wherein said ligand and said candidate binding protein are bound in said bacterium. The claimed method in this application encompasses a genus of bacteria comprising nucleic acid sequences encoding a binding protein that are capable of a target ligand and application 10, 620,278 encompasses a particular species of bacteria comprising nucleic acid sequence encoding a binding protein having specific affinity for a target ligand. The method claimed in this application would encompasses the scope of the method claimed in co-pending application 10/620,278. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant urges that the terminal disclaimer will be filed upon indication of allowable subject matter.

Applicant's arguments filed August 16, 2005 have been fully considered but they are not persuasive. Applicant must file a terminal disclaimer or amend the claims to obviate this rejection. It should be noted that no allowable subject matter has been indicated.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

6. Claims 1-2 and 4-32 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-2 and 4-32 are drawn to a method of obtaining a bacterium comprising a nucleic acid sequence encoding a candidate binding protein capable of binding a target ligand comprising the steps of:

(a) providing a gram-negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein wherein said binding protein is expressed in soluble form in the periplasma of said bacterium;

(b) contacting said bacterium with a labeled ligand that diffuses into said periplasm; and;

(c) selecting said bacterium based on the presence of said labeled ligand within the periplasm, wherein said ligand and said candidate binding protein are bound in said bacterium.

The claims are drawn to a method that uses a vast genus of candidate binding proteins. The claimed method utilizes gram-negative bacteria comprising nucleic acid molecules that encode candidate binding proteins of "any" molecular weight. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

To adequately describe the genus of candidate binding proteins one must describe the ligands that bind to a said binding proteins wherein said ligands are lableled and are capable of diffusing into the periplasmic space of a gram-negative bacterium. However, the specification has not provided written description for all labeled ligands to the candidate binding proteins that are encompassed by the claimed invention, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Moreover, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of ligand to the candidate

binding proteins that can be used in the claimed method. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of labeled ligands on which the claims are based; the specification fails to adequately describe at least a substantial number of members of the genus of candidate binding proteins in the claimed method. The specification does not teach that what ligands are capable of diffusing into the periplasm since said ligands are not characterized Ames et al discloses that molecules of molecular weight greater than the exclusion limit of about 650 Da to about 900 Da can cross and enter into the periplasm or cytoplasm of a gram-negative bacteria cell without facilitated transport. The specification fails to provide written description for the use of "labeled ligands" that have a molecular weight of about 5,000 dalton or about 20,000-30,000 daltons as required by the claim limitations of claims 18-20.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement

provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104).

Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Ames *(Journal of Bioenergetics and Biomembranes, Feb., 1988, 20(1) 1-17)* teaches that bacterial periplasmic transport systems are complex, multicomponent permeases present in gram-negative bacteria. Ames teaches that the cell wall proper is commonly regarded as a widely open entirely permeable layer which confers rigidity and through which nutrients diffuse readily and the cytoplasmic membrane is impermeable to almost every solute unless a special transport system is provided (page 2). Decad et al, *(Journal of Bacteriology, October 1976, 128(1):325-36).* teach that only disaccharides and trisaccharides could fully diffuse into the periplasm, whereas higher molecular weight saccharides were non-penetrable. Decad et al teach that the cell wall acts as a molecular sieve with an exclusion limit near 550 to 650 daltons for saccharides (see the Abstract). Nakae et al *(The Journal of Biological Chemistry, Vol. 250, No.18, September, 1975)* teach that the both the outer membrane and the peptiodoglycan layer of gram-negative bacteria acts as a barrier of the molecular sieve type for the penetration of uncharged saccharides (see the Abstract). Nakae et al teach that the exclusion limit for *E. coli* and *Salmonella typhimurium* is about 900 daltons or less for saccharides which is much smaller in comparison to gram-positive bacteria which is about 100,000 daltons for *Bacillus megaterium* (page 7363).

Therefore, the prior art teaches that non-facilitated transfer (i.e. diffusion) of compounds across the outer membrane has an exclusion limit of about 650 to about 900 daltons.

Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of candidate binding proteins, the skilled artisan could not immediately recognize or distinguish members of the genus of candidate binding protein used in the claimed method.

In view of the above, the instant specification fails to meet the written description in regards to the genus of candidate binding proteins used in the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2 and 4-32 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble of claim 1 recites "A method of obtaining a bacterium...". Step (a) of claim 1 provides "providing a gram-negative bacterium...". It is unclear is as to what Applicant intends since the method is directed obtaining a bacteria and the first step in the method provides the bacterium. Clarification/correction is required.

8. Claims 1-2 and 4-32 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (step (c) recites "selecting said bacterium...". It is unclear is as to what Applicant as to how the bacterium is selected since there is no step to collected the bacterium. Clarification/correction is required.

9. Claims 1-2 and 4-32 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (step (c) recites "... wherein said ligand and aid candidate binding protein are bound in said bacterium". It is unclear is as to what Applicant as which ligand Applicant is referring since the claim recites both a "target ligand" and a "labeled ligand". Clarification/correction is required.

Status of Claims

10. No claims allowed.

Conclusion

11. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
November 8, 2005

ROBERT A. ZEMAN
PATENT EXAMINER